

REMARKS

Claims 5, 9-16, 19-23, 26 and 30-64 are pending and under examination in the subject application. Claims 5, 9-16, 19-23, 26, 30-34, 39, 41-53, 54-58 and 60 have been amended above. Support for the amendments can be found throughout the application and claims. In particular, support for the amendment to claims 5, 26, 32, 33, 39, 54, 57 and 58 can be found at, for example, page 7, lines 8-13, in claims 5, 32, 39 and 57 at original steps (b)-(d) and in claims 26, 33, 54 and 58 at original steps (b)-(e). Claims 5, 32, 39 and 57 also have been amended to recite the additional step of immobilizing the ligation complex to a solid support. Support for the amendments can be found at, for example, page 21, line 18 through page 24, line 16, and particularly at, for example, page 23, lines 16-17. Claims 9-16, 19-23, 30, 31, 34, 41-53, 55, 56 and 60 have been amended to correct informalities pointed out in the Office Action mailed March 23, 2006, and in the subsequent Office Communication mailed November 30, 2006. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the rejections set forth in the Office Action mailed March 23, 2006, and respectfully traverse all grounds for the reasons that follow.

Applicants would like to thank Examiner Lu for extending a personal interview with Applicants' representatives on August 21, 2006. In particular, Applicants' representatives discussed with Examiner Lu amendments to the claim which further distinguish the cited art. Applicants' representatives also pointed to the nonobviousness of the claimed invention over the cited art. The amendments above and remarks below are believed by Applicants to substantially conform to the subject matter discussed in the interview.

Formalities

Claims 9-16, 19-23, 30, 31, 34, 41-53, 55, 56 and 60 have been amended above to correct the informality noted in the Office Communication mailed November 30, 2006. All other amendments and remarks set forth herein are identical to those filed in Applicants' Response mailed September 15, 2006, and have been reiterated for the Examiner

Rejections Under 35 U.S.C. § 112

Claims 5, 26, 32, 33, 39, 54, 57 and 58 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office asserts that steps (e) and (f) of these claims are unclear allegedly because the claims do not require the plurality of amplicons to contain an adaptor sequence.

Applicants submit that the claims as written are sufficiently clear to those skilled in the art to satisfy the requirements of § 112, second paragraph. The claims recite hybridizing first and second ligation probes containing five portions to a target sequence wherein the fifth portion corresponds to an adapter sequence to form a ligation complex. Immobilizing formed ligation complexes, ligating the ligation probes to form ligated probes and amplifying the ligated probes to generate a plurality of amplicons. Because ligation probe sequences including adapter sequences becomes incorporated into the amplicons it is clear to those skilled in the art that the amplicons also contain the incorporated adapter sequence. Nevertheless, to further prosecution Applicants have amended claims 5, 26, 32, 33, 39, 54, 57 and 58 to specifically recite that each amplicon within the plurality of amplicons contains an adapter sequence as suggested by the Examiner. Accordingly, this ground of rejection is moot and its withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 5, 13, 32, 39, 45 and 57 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Barany et al., U.S. Patent No. 6,534,293. The Office alleges Barany et al. describe detection of nucleic acid sequence differences using coupled ligase detection and polymerase. Figure 60; column 80; claim 1; page 13, lines 14-15, and page 19, para. 3 are cited as support for allegedly describing the invention as claimed.

Applicants respectfully submit that Barany et al., the '293 patent, does not teach all elements of the claimed invention. Nevertheless, to further prosecution, Applicants have amended the claims to recite after step (b) that the ligation complexes are immobilized to a solid support. Therefore, the claimed invention recites immobilization of both the ligation complexes to a solid support and capturing the amplicons with an array of capture probes. Barany et al., the

'293 patent, does not describe both of these immobilization steps. Accordingly, the claimed invention is distinct from Barany et al., the '293 patent, and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Dependent claims 14-16, 34, 46-48 and 60 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al., U.S. Patent No. 6,027,889, in view of Walt et al., U.S. Patent No. 6,327,410. The Office concedes that Barany et al., the '889 patent, does not disclose the array as claimed, but alleges that one skilled in the art would have been motivated to use the array described by Walt et al. because the replacement of one array type with another type would not change the steps of the experiment.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03. Applicants submit that the cited references fail to teach or suggest all elements of the claimed invention.

The base claims for claims 14-16, 34, 46-48 and 60 recite the step of immobilizing the ligation complexes to a solid support. Therefore, the claimed invention recites immobilization of both the ligation complexes to a solid support and capturing the amplicons with an array of capture probes. Barany et al., the '889 patent, and Walt et al., neither teach or suggest the inclusion of both of these steps in a method of determining the identification of a nucleotide at a detection position. In the absence of a teaching or suggestion in the cited references of each element of the claimed method, the Office has not established a *prima facie* case of obviousness of the rejected claims under 35 U.S.C. § 103(a). Therefore, Applicant's respectfully request withdrawal of this ground of rejection.

Claims 26, 33, 54, 58 and dependent claims 10, 13, 19-22, 31, 35, 42, 49-52, 56, 59 and 61 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al., U.S. Patent No. 6,027,889 (1997) in view of Zhang et al., U.S. Patent No. 5,876,924. The Office concedes that Barany et al. does not describe step (a) of claims 26, 33, 54 and 58, directed to providing a support on which the target sequence is immobilized, but alleges that the streptavidin beads

described by Zhang et al. provide this element since the claimed steps are not required to be performed in order. Alleging that there is no invention in combining old elements that perform the same function set forth in the art absent unobvious or unexpected results, the Office concludes that one skilled in the art would have been motivated to replace the ligation method of Barany et al. with the method described by Zhang et al. because the two methods are “equivalent” and “used for the same purpose.” Further motivation for the substitution of one method with the other is alleged because the elements within each method would be expected to “achieve their expected results” when “combined for their common known purpose.” Office Action mailed March 23, 2006, page 9, first paragraph through page 10, first paragraph.

Applicants respectfully disagree.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03.

Applicants reassert their arguments of record. The claimed invention expressly recites generating a plurality of amplicons where each amplicon contains a fifth portion having an adapter sequence that is distinct from the first, second, third and fourth portions of the claimed ligation probes. Because the fifth portion is distinct from other portions of the ligation probe it cannot specifically hybridize to the target sequence. Therefore, the claimed ligation probes are distinct from the probes of Barany et al., which hybridize to the target sequence. The capture/amplification probe described by Zhang et al. also fails to describe specific hybridization with an adapter sequence because it uses ligand binding probes and because the alleged fifth portion is arbitrary and does not appear to hybridize to anything specific. Rather, this alleged fifth portion appears to be a physical label moiety. As set forth further below, the combination of Zhang et al. for allegedly describing a solid support or for providing motivation for the substitution of allegedly similar amplification methods fails to cure the above deficiencies. Accordingly, absent a teaching, suggestion or motivation to use a capture probe that specifically hybridizes to an adapter sequence, the claims cannot be obvious over the cited art because the cited combination of references fail to provide the requisite teaching, suggestion or motivation for combining all elements of the claimed invention.

Applicants claim a method of determining the identification of a nucleotide at a detection position in a target sequence that includes both the immobilization of a target sequence prior to amplification and then immobilization of amplicons by capture with an array. The Office's conclusion that the "replacement" or "substitution" of one method for the other method to arrive at the claimed invention because the two cited methods are "equivalent," "used for the same purpose" or expected to "achieve their expected results" is deficient with respect to its application to the claimed invention.

As Applicants pointed out during the interview of August 21, 2006, the question is not whether the cited combination of Barany et al. and Zhang et al. provide a teaching, suggestion or motivation to replace or substitute the method of Barany et al. with Zhang et al. to achieve immobilization of a target sequence as claimed in step (a) and conceded to be absent in Barany et al. Both Barany et al. and Zhang et al. describe a single attachment step. Rather, the question is whether:

One of ordinary skill in the art at the time of the invention would have been motivated to combine a first immobilization step of a target sequence with a second immobilization step for capture and detection because the two methods are "equivalent" and "used for the same purpose."

When viewed in light of the claim as a whole, a *prima facie* case of obviousness has again not been established because the teaching, suggestion or motivation has been omitted.

First, there has been no showing that the two methods are equivalent, used for the same purpose or expected to achieve their expected results such that one skilled in the art would arrive at the claimed first immobilization step of the target sequence with a second immobilization step for capturing and detection. The Office asserts that the cited references describing equivalent methods that employ a single immobilization step renders the invention obvious. However, the claims recite both a first immobilization step of the target sequences and a second immobilization step for capture of amplicons with an array. Equivalency of one method employing a single immobilization step with another method also employing a single immobilization step would indicate to one skilled in the art that any combination of the two equivalent methods would also result in method that similarly employs a single immobilization step. The Office has failed to point out in the cited references where the two methods used for

the same purpose would teach, suggest or motivate one of ordinary skill in the art to arrive at the claimed first and second immobilization steps. Rather, equivalency of the methods described in the cited art point to the opposite conclusion of maintaining a single immobilization step.

Second, the Office's apparent reasoning that "replacement" or "substitution" of one method for the other is sufficient to sustain an obvious rejection is unsupported by in the references or by the proffered rationale. To arrive at the claimed invention one skilled in the art would be required to modify one method with elements of the other method to arrive at a third, non-equivalent method. Replacement or substitution, without more, fails to teach, suggest or provide the requisite motivation to arrive at the claimed invention because replacement or substitution of one method for another method used for the same purpose would yield the same result - namely, for producing hybridization probes using a single immobilization step (see, for example, Office Action mailed March 23, 2006, at p.9, para.1). The Office has not pointed to any teaching or suggestion that would motivation one of ordinary skill to modify either or both single immobilization methods to generate a new method containing two immobilization steps. The mere assertion that the two methods can be substituted because they are equivalent and used for the same purpose fails to satisfy this requirement under § 103(a).

Third, the law is clear with respect to the requirements for properly combining references. Simply identifying elements in the cited art fails to render a claimed invention obvious absent a specific reason to do so. Here, because the methods are conceded to be equivalent, there can be no specific reason to combine to arrive at a third, and different, method.

During the personal interview conducted August 21, 2006, Applicants' representative pointed to the recent authority which particularly sets forth the required analysis for establishing motivation to combine when the claimed combination of elements are alleged to be found across several references. The "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." *In re Kahn*, Case No. 04-1616, slip op. at p.11 (Fed. Cir. March 22, 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). Further, *In re Kahn* emphasized that to guard against hindsight, the motivation of one of ordinary skill in the art to combine must be explained. *Id.*, slip op. at pp.11-12. The Court explained further that in the motivation analysis, the problem examined is "the general

problem that confronted the inventor before the invention was made.” *In re Kahn*, Case No. 04-1616, slip op. at 15 (citing *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323 (Fed. Cir. 2005)). However, “[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.” *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (internal citation omitted) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

One problem facing the inventor solved by the claimed invention is directed to providing a flexible assay for accurate determination and quantitation of target sequences in a variety of different settings (see, for example, Application at page 6, lines 1-6; lines 23-25 and page 7, lines 14-19). There is nothing in the cited art or in the equivalency, use for the same purpose, replaceability or substitutability of the methods described in the cited art which provides the motivation to arrive at the claimed invention as a solution to this problem facing the inventor. Both cited references are directed to detection of nucleic acid sequences and describe a specific detection format that includes a single immobilization step. Neither reference provides any indication that inclusion of multiple immobilization steps will provide any advantage or even a desirable result. Rather, both Barany et al. and Zhang et al. describe methods of detection employing a single immobilization step. Therefore, no alternatives are taught or suggested in either Barany et al. or Zhang et al. that include use of a second immobilization step as is claimed by the invention, whether to provide a flexible assay for accurate determination and quantitation of nucleic acid sequences as taught in the specification or for any other reason. Hence, the Office’s conclusion appears to be a hindsight reconstruction focusing on the solution and ignoring the requirement for a teaching, suggestion or motivation for establishing a *prima facie* case of obviousness through a combination of art.

The cited combination further appears to be an improper hindsight analysis because there also is no motivation to modify one method describing a single immobilization step with another method which also describes a single immobilization step to arrive at two different immobilization steps absent a specific reason to do so. Both Barany et al. and Zhang et al. may, *arguendo*, be considered to be skilled in the art of nucleic acid detection. However, neither reference suggests the possibility of modifying either method to contain two separate immobilization steps. As evident from both Barany et al. and Zhang et al., those which might be

considered to be skilled in the art, failed to even contemplate that inclusion of multiple immobilization steps would be beneficial. Neither the Office nor any of the cited references provide any explanation why one of ordinary skill would be motivated to arrive at a method that contains two different immobilization steps. The simple explanation that the two methods are equivalent or substitutable improperly views the problem from the solution as it is claimed by the invention, rather than to view it from the problem facing the inventor at the time of the invention, and constitutes hindsight. Absent any showing that the cited references themselves teach or suggest the claimed invention or, based on the combination of references, absent a particular articulation of why one of ordinary skill in the art would be motivated to arrive at the claimed invention employing a first immobilization step for the targets and a second immobilization step for the amplicons, Barany et al. and Zhang et al. fail to render the invention obvious for merely describing certain elements of the claimed invention.

Applicants maintain that the current rejection fails to articulate a *prima facie* case of obviousness because the motivation, teaching or suggestion has been omitted. The Office's analysis appears to have been incorrectly applied to the solution of the inventor's problem rather than to the problem itself. Applicants maintain that they have met their burden and that a finding of allowability should be rendered.

Claims 11, 12, 43 and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al. as applied above and further in view of Gebeyehu et al., U.S. Patent No. 4,921,805. Gebeyehu et al. is cited for allegedly describing an intercalator attached to a bead to separate non-hybridized probes from hybridized probes as claimed. Similarly, claims 9, 23, 30, 41, 53, and 55 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., as applied above, and further in view of Seradyn Particle Technology. Claims 37 and 63 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., and further in view of Monforte et al., U.S. Patent No. 5,830,655. Claims 36 and 62 stand rejected under 35 U.S.C. § 103(a) over the above combination of references and further in view of Brown et al., U.S. Patent No. 5,807,522, whereas claims 38 and 64 stand rejected under 35 U.S.C. § 103(a) over the combination of Barany et al. in view of Zhang et al. and Monforte et al. and further in view of Johnson et al.

All of the above claims depend from one or more of the independent claims 5, 26, 32, 33, 39, 54, 57 and 58. Accordingly, the dependent claims contain all the limitations of the base claims from which they depend. As set fourth above, neither Barany et al. in view of Walt nor Barany et al. in view of Zhang et al. provide all elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to teach, suggest or provide a motivation for each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Gebeyehu et al., Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references. Accordingly, the cited art cannot teach or suggest all elements of the claimed invention and withdrawal of this ground of rejection is respectfully requested.

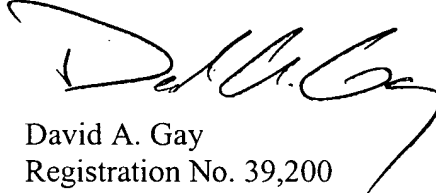
CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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